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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,747	12/21/2005	Maurice Raymond Verschoyle Finlay	06275-487US1 101094-1P US	5927

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EXAMINER	
LEESER, ERICH A	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,747	FINLAY ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,20-26 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29-31* is/are allowed.

6)☒ Claim(s) *1-17,20-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *December 18, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17, 20-26 and 28-31 are pending and under examination.

Priority

Acknowledgment is made that this application is a 371 of PCT/GB04/02702, filed June 23, 2004, which claims foreign priority to SWEDEN 0301922-1, filed on June 27, 2003.

Information Disclosure Statement

The references cited in the IDS, dated December 18, 2006, are made of record.

Specification

The title is objected to as it inadvertently includes a "!". It is improper to include exclamation marks in compound names. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 20-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making prodrugs or solvates of the claimed compounds. The claims contain subject matter that is not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to make and use the invention.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention

The invention is drawn to compounds or a "pharmaceutically acceptable salt, prodrug or solvate thereof." The specification is not adequately enabled to show how to make prodrugs or solvates of the compounds of the present invention.

The compounds of the present invention embrace heterocyclic compounds with variable groups ring B, R_1 and R_2.

Even a cursory calculation of the number of compounds embraced in the instant claim 1 would result in thousands of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. Thus, the genus embraced in claim 1 is too large and there is no teaching of any prodrug or solvate of compounds or compositions of this large genus.

The state of the prior art:

The state of the prodrug art is summarized by Wolff, Manfred E., *Burger's Medicinal Chemistry and Drug Discovery*, Fifth Ed., Vol. 1: Principles and Practice, John Wiley & Sons, 1995, 975. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating

between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker, Gilbert S. et al., *Modem Pharmaceutics*, Marcel Dekker, New York, 1996, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

The predictability or lack thereof in the art:

It is well-established that "the scope of enablement varies inversely to the degree of unpredictability of the factors involved", "and physiological activity is generally considered to be an unpredictable factor." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for

example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

The amount of direction or guidance present:

The amount of guidance or direction refers to that information in the application that teaches exactly how to make or use the invention. The specification contains no working examples of a prodrug or solvate of a compound of the present invention. Examples illustrated in the experimental section are limited to making the compounds of the invention, but not their prodrug or solvate forms of those same compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance. Thus, undue experimentation will be required by one skilled in the art to make the prodrugs and solvates of the claimed invention.

The presence or absence of working examples:

The specification contains no working examples of a prodrug or solvate of a compound of the present invention. These cannot be simply willed into existence. "The specification

purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that prodrugs and solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that prodrugs and solvates of these compounds exist and therefore can be made. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug or solvate.

The breadth of the claims:

The breadth of the claims includes all of the thousands of compounds of claim 1 and compositions of claim 16 as well as the presently unknown list of potential derivatives embraced by the claim terms prodrug and solvate. The terms are important in claim 1 and 16 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed prodrugs and solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the prodrugs and solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

Substantial and undue experimentation would be needed to practice Applicant's invention because the specification lacks sufficient detail to show how to use the prodrugs and solvates of the instant invention. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired prodrugs and solvates of the compounds embraced in the instant claims. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to treat a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis with a therapeutically-effective amount of a compound of claim 1 or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of

the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to compounds used to treat a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis with a therapeutically-effective amount of a compound of claim 1.

The state of the prior art:

The relevant scientific community has revealed a new class of spiro-barbiturates (e.g., 4a, MMP-13 K(i)=4.7 nM) that are potent inhibitors of MMP-13, but Examiner could not find any peer review article demonstrating the therapeutic applicability of Applicant's piperazine compounds: Kim Soong-Hoon, et al., *Structure-based design of potent and selective inhibitors of collagenase-3 (MMP-13)*, Bioorganic & medicinal chemistry letters, (2005 Feb 15) Vol. 15, No. 4, pp. 1101-6.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly

unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of claim 1 would be useful to treat a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis.

Amount of guidance/working examples:

The specification does not definitively show that the instant compounds can reliably be used to treat a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis with a therapeutically-effective amount of a compound of claim 1.

The breadth of the claims:

The claim terms "disease condition mediated by collagenase 3" in claim 20 and "metalloproteinase mediated disease condition" in claim 25 are unduly broad because a reader would not have any idea as to the metes and bounds of these claim terms as to what disease conditions they include and exclude.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient for the treatment of a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis with a therapeutically-effective amount of a compound of claim 1, one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to make and use Applicant's invention for treating a disease condition mediated by collagenase 3, an obstructive airways disease, osteoarthritis, atherosclerosis, a metalloproteinase mediated disease condition or rheumatoid arthritis with a therapeutically-effective amount of a compound of claim 1 without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected if it is dependent on a rejected claim and shares the same indefiniteness.

(a) Although the structure of formula (I) in claim 1 designates "R_1", the text of the claim provides the definition of the variable group as "R1." Correction of this inconsistency is required.

(b) The period of claim 9 was inadvertently excluded. Correction is required.

(c) The steps of process claim 28 are unclear. Specifically, the modifier "appropriate" modifying "mixed anhydride" is unclear in that how would a reader know what is and what is not an appropriate mixed anhydride? Clarification is required.

(d) Claim 28 states, "converting the compound obtained into a further compound" without providing any description whatsoever as to the structure of either of these compounds. Clarification is required.

(e) Claim 28 also states, "according to the invention" without describing what one skilled in the art would do to carry out this step to prepare the compounds of claim 1. Clarification is required.

Claim Rejections 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

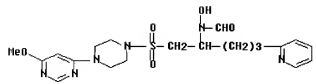
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

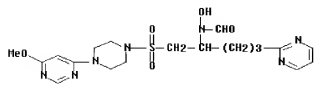
Claims 1-3, 8-11, 14, 16-17 and 23-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Barlaam, et al., U.S. Patent No. 6,734,184.

Barlaam, et al., teaches arylpiperazine compounds as metalloproteinase inhibiting agents and also teaches that the class of compounds of which compounds of instant formula (I) belongs is limited to a finite number of compounds within the class. Generically, claim 1 of the reference renders the scope of instant claim 1 obvious.

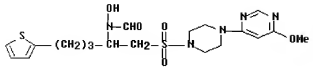
For example, a compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is pyrimidinyl, R1 is C3alkyl-heteroaryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-5-(2-pyridinyl)pentyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



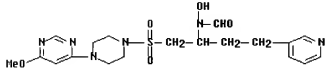
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is pyrimidinyl, R1 is C3alkyl-heteroaryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-5-(2-pyrimidinyl)pentyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



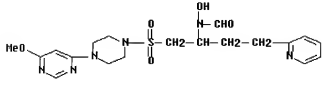
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is pyrimidinyl, R1 is C3alkyl-heteroaryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-5-(2-thienyl)pentyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



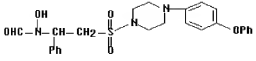
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is pyrimidinyl, R1 is C3alkyl-heteroaryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-4-(3-pyridinyl)butyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



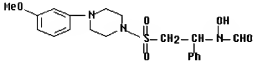
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is pyrimidinyl, R1 is C2alkyl-heteroaryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-4-(2-pyridinyl)butyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



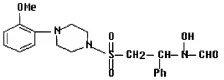
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is a monocyclic aryl ring having six ring atoms, R1 is aryl and R2 is aryl: 1-[[2-(formylhydroxyamino)-2-phenylethyl]sulfonyl]-4-(4-phenoxyphenyl)-piperazine with the following formula:



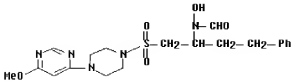
A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is a monocyclic aryl ring having six ring atoms, R1 is aryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-2-phenylethyl]sulfonyl]-4-(3-methoxyphenyl)-piperazine with the following formula:



A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is a monocyclic aryl ring having six ring atoms, R1 is aryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-2-phenylethyl]sulfonyl]-4-(2-methoxyphenyl)-piperazine with the following formula:



A compound of instant formula (I) is rendered obvious by the reference when n is 1, ring B is a pyrimidinyl, R1 is C2alkyl-aryl and R2 is C1alkyl: 1-[[2-(formylhydroxyamino)-4-phenylbutyl]sulfonyl]-4-(6-methoxy-4-pyrimidinyl)-piperazine with the following formula:



Therefore, it would have been obvious to an ordinary pharmaceutical chemist to try the compounds of Barlaam, et al. in an attempt to provide an improved formulation of the class of compounds to which instant formula (I) belongs, as a person skilled in the art has good reason to pursue the known options within her or his technical grasp.

Thus, it would have been obvious to one having ordinary skill in the art at the time that the invention was made to make similar compounds of Barlaam, et al.

Allowable Subject Matter

Claims 29-31 are patentable over Barlaam, et al., U.S. Patent No. 6,734,184, which teaches arylpiperazine compounds as metalloproteinase inhibiting agents. The difference between the compounds of the closest prior art and the instant compounds is that the instant compounds require the presence of R2 substituted with "one or more fluorine groups," which is neither taught nor suggested by the reference. Therefore, the claims are free of prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/James O. Wilson/
Supervisory Patent Examiner
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